**ANRS EP 57 - APACHES**- Information for researchers

**Title** : ANRS EP57 APACHES Natural history of anal human papillomavirus infection and associated disease in HIV-infected men who have sex with men: towards an evidence base for the prevention of anal cancer.

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| In brief | Investigator: Isabelle ETIENNEY |
| | Structure/teams :<br>- Centre international de Recherche sur le Cancer (Dr Gary CLIFFORD)<br>- Groupe hospitalier Diaconesses Croix Saint-Simon (Dr Isabelle ETIENNEY) |
| | Start dates : 2nd December 2014<br>End date of research: 30th Jun 2022 |
| | Number of participants recruited : 513 |
| | Research status: completed |
| | Pathology: HIV/ANAL CANCER |
| | Promotion: Inserm - ANRS MIE |
| | Funded under: AAP 2013-2 |
| The project | Persons living with HIV, particularly men having sex with men, have a high burden of HPV-related anal cancer. At the time of initiation of this study, although screening for anal cancer in persons living with HIV (PLHIV) had been proposed, using cytological, virological or other biomarkers to detect and treat the presumed anal cancer precursor, anal intraepithelial neoplasia (AIN)2/3. However, little was known about the natural history of anal HPV infection and AIN2/3, nor the efficiency of algorithms for anal cancer screening. Objectives: To characterise the natural history of anal HPV infection and related lesions among ¬500 HIV-infected homosexual men aged 35 years across France (Paris, Marseille, Lyon, Rennes, dijon and Montpellier), we proposed to: 1) Determine the prevalence, incidence and persistence of type-specific anal HPV DNA and cytological abnormalities. 2) Evaluate markers of transforming HPV infection (HPV type, p16/Ki67 staining) as predictive factors for AIN2/3, confirmed histologically via the use of high-resolution anoscopy (HRA), and their utility as screening tests. 3) Observe the rate of, and characterise predictive markers for, the regression and/or re-occurrence of AIN2/3, followed by watchful waiting before treatment. Perspectives: Study results were expected to inform guidelines for anal cancer screening in HIV-positif homosexual men in France and elsewhere (which they did - see below). |
| Latest news | Since publication of APACHES findings, first French recommendations for anal screening have been published (Spindler L, Société Nationale Française de Colo-Proctologie, Tech Coloproctol. 2024), including for persons living with HIV (Recommandations de dépistage et prise en charge des cancers chez les personnes vivant avec le VIH, des hépatites virales et des IST : rapport d'experts, https://cns.sante.fr/wp-content/uploads/2024/06/VIH-Cancer_Recommandation_Rapport-dexperts_-20240521.pdf) |

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| Publication references | <u>Findings from baseline visits:</u><br>1) Determinants of high-grade anal intraepithelial lesions in HIV-positive MSM. Clifford GM et al, AIDS. 2018<br>2) Prevalence and Risk Factors for Anal Human Papillomavirus Infection in Human Immunodeficiency Virus-Positive Men Who Have Sex with Men. Combes JD et al, J Infect Dis. 2018<br><br><u>Findings from 2 year follow-up:</u><br>3) Incidence and Clearance of Anal Human Papillomavirus (HPV)-16 and HPV-18 Infection, and Their Determinants, Among Human Immunodeficiency Virus-Infected Men Who Have Sex With Men in France. Alberts CJ, J Infect Dis. 2020<br>4) Cumulative Detection of Anal High-Grade Squamous Intraepithelial Lesions Over 2-Year Follow-up in Men Who Have Sex With Men Living With Human Immunodeficiency Virus in France. Combes JD et al. J Infect Dis. 2024<br><br><u>Preliminary findings from 5-year follow-up of anal HSIL:</u><br>5) PERSISTENCE AND CLEARANCE OF HISTOLOGICAL ANAL HIGH-GRADE LESIONS IN MEN WHO HAVE SEX WITH MEN LIVING WITH HIV. Clifford GM et al. Abstract. International Papillomavirus Conference. Edinburgh. 2024.<br><br><u>Contribution of baseline data to larger pooled analyses :</u><br><br>6) Incidence and Clearance of Anal Human Papillomavirus Infection in 16 164 Individuals, According to Human Immunodeficiency Virus Status, Sex, and Male Sexuality: An International Pooled Analysis of 34 Longitudinal Studies. Wei F, et al. Clin Infect Dis. 2023<br>7) Epidemiology of anal human papillomavirus infection and high-grade squamous intraepithelial lesions in 29 900 men according to HIV status, sexuality, and age: a collaborative pooled analysis of 64 studies. Wei F et al Lancet HIV. 2021<br>8) A systematic review and meta-analysis of cytology and HPV-related biomarkers for anal cancer screening among different risk groups. Clarke MA, Int J Cancer. 2022 |
| Main objectives | To characterise the natural history of anal HPV infection and related lesions among HIV-infected homosexual men aged 35 years across France. |
| Secondary objectives | - Assess the frequency of spontaneous regression of high-grade anal lesions.<br>- Evaluate markers predictive of detection and regression of high-grade anal lesions and their utility as screening tests.<br>- Assess the prevalence, incidence and persistence of anal HPV infection. |
| Optional: Link to research website | NA |
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| **Inclusion criteria** | - Men who have sex with men<br>- At least 35 years old |

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| | - HIV-positive (documented search of HIV infection, with HIV status determined according to HAS algorithm)<br>- Signed informed consent<br>- Affiliated to or beneficiary of French social security<br>All severity criteria and evolution of HIV disease are accepted (including AIDS stage and co-infections) |
| **Non-inclusion criteria** | - Contraindication to biopsy<br>- History of anal cancer or pelvic radiotherapy<br>- AIN2/3 treated during previous year<br>- Current anticancer chemotherapy or within 24 months before inclusion<br>- Difficulty in evaluation (anus reshaped and/or scarred)<br>- Individual placed under judicial protection (French “tutelle”, “curatelle”, “sauvegarde de justice”)<br>- Foreseen absence which may hamper participation; insufficient motivation; associated pathology with priority for care |
| **Primary endpoints** | • Detection of high-grade cytological and histological anal lesions by high resolution anoscopy<br>• Regression of high-grade anal lesions<br>• Detection of anal HPV infection |
| **Secondary endpoints** | Pathology: VIH/CANCER |

Contents



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## A - Study methodology and type of data and/or samples collected

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| **Data and samples collected** | **Biotech libraries** | Aliquots of DNA/RNA extracted form anal cytology aliquots. |
| | **Data** | HIV-related history (CD4, CD8, viral load, ART etc). AIDS-defining conditions,<br>Recruitment center (1-6), Age, Tobacco.<br>Lifetime receptive genito-anal sexual partners, receptive genito-anal sexual partners last year, History of previous anal swab and/or biopsies, anal cytology result, Anal biopsy histology, Anoscopy impression.<br>Human Papillomavirus detection from anal swabs (using Cobas4800) systematically from visits M0, M12 and 24. Full HPV |

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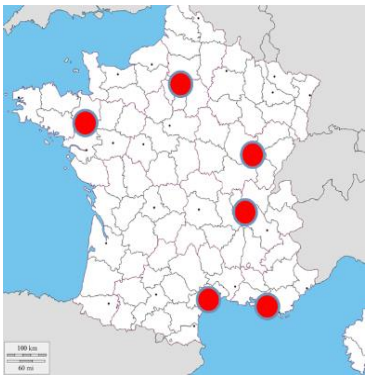
| | | genotyping (using Papillocheck test) at M0 only.<br>Anal cytology results from visits m0 – M60.<br>Histology results from anal biopsies from visits m0 – M60. |

6 recruitment centers in France (Paris, Marseille, Rennes, Lyon, Montpellier, Dijon)



Prospective study:

Follow-up 2 years if no high-grade lesion detected

Follow-up 5 years if high-grade lesion detected

All patients (n=513 patients), at all visits :

Anal swab (Rovers Anex brush)

High resolution Anoscopy (HRA) +/- biopsy if lesion

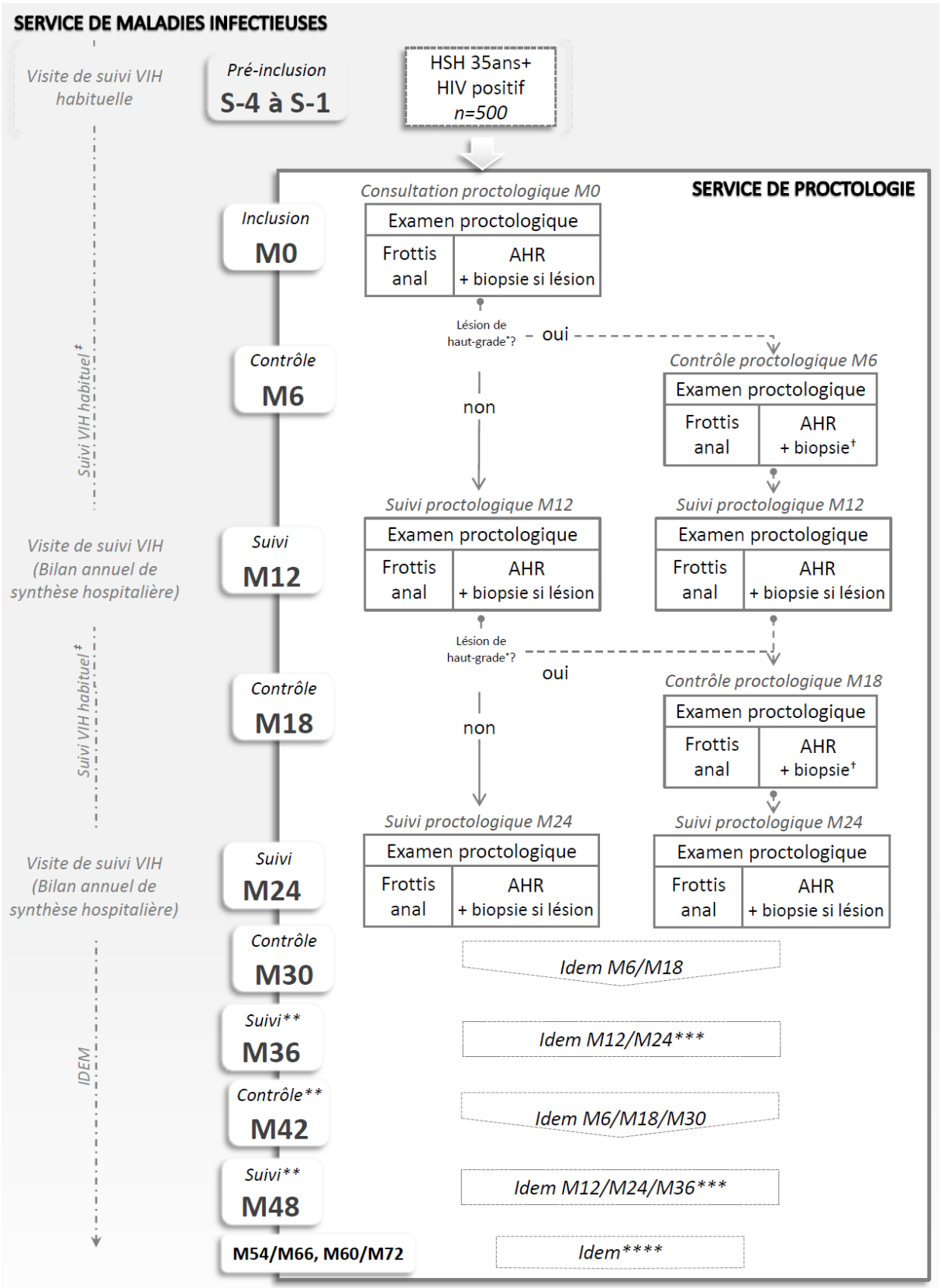
Follow-up of each visualised/biopsied lesions (HG or non-HG) separately

If HG cytology or histology, intermediate surveillance visits every 6 months (same protocol, usually no biopsies)

APACHES High-grade (HG) sub-population (n=110 patients) = those with at least one HG cytology or histology during APACHES I (=M0-M24)

Same protocol at each visit (anal swab, HRA +/- biopsy)

**Schemas**



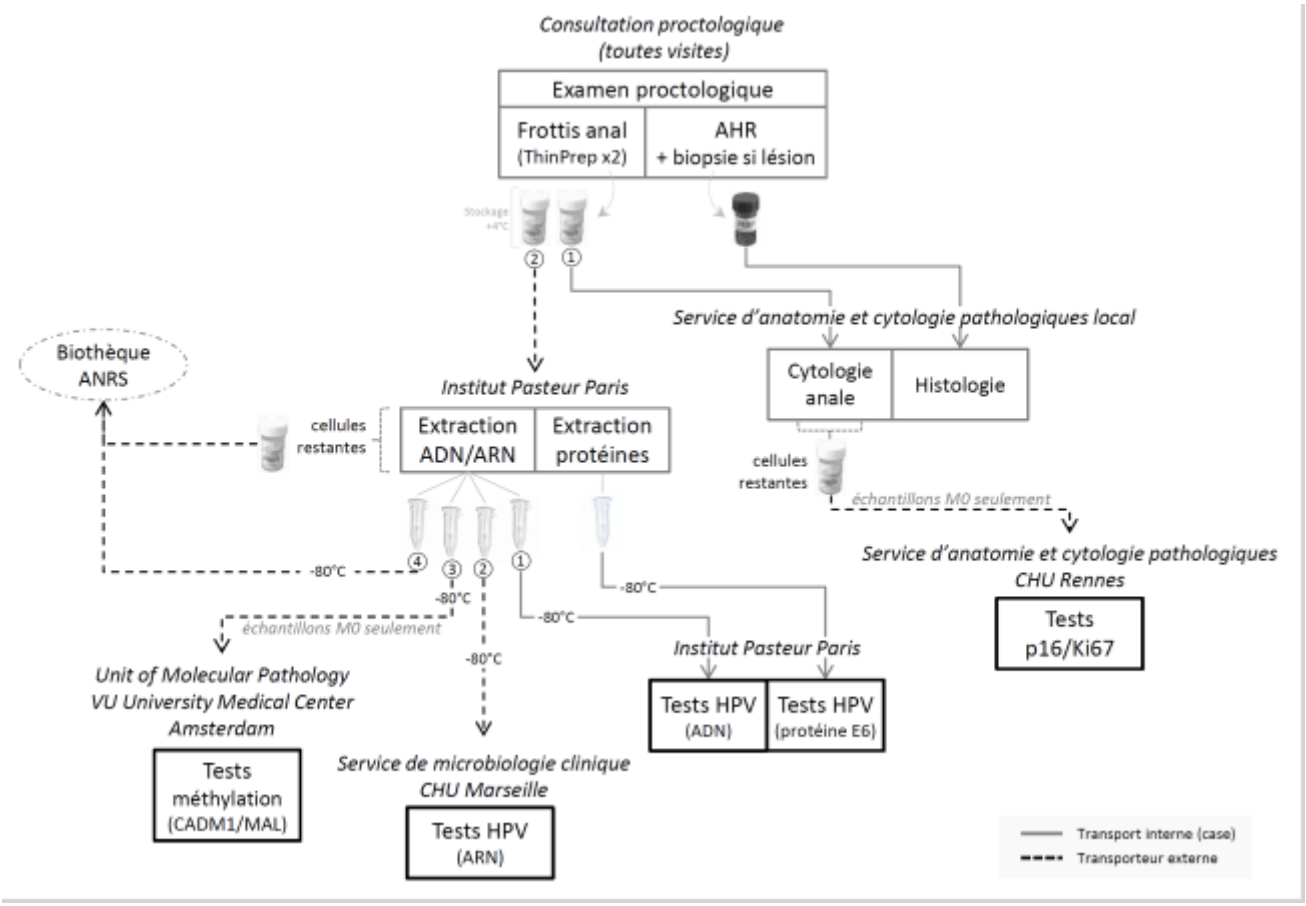

* Lésion de haut-grade = ASC-H ou HSIL ou AIN2 ou AIN3
† Seulement si nouvelle lésion ou modification importante d'une lésion existante
‡ Suivi VIH habituel : visites trimestrielles ou semestrielles (libéral ou hospitalier)
** ou visite de fin de recherche, selon date d'inclusion (cf. protocole 9.5)

*** si aucune lésion de haut-grade diagnostiquée lors d'une visite antérieure, pas d'AHR systématique pour les visites de suivi à partir du 1e juillet 2018 (cf. 9.5)
**** à partir du 1e juillet 2019, suivi uniquement des patients avec lésion de haut-grade diagnostiquée précédemment (cf. protocole 9.5)

**Ajouter le calendrier des prélèvements si applicable**

| | **Pre-inclusion** | **Inclusion** M0 | **Visites de contrôle** M6/M18/M30/M42/M54 (+/-M66*) | **Visites de suivi** M12/M24/M36/M48/M60 (+/- M72*) |
|---|---|---|---|---|
| **Service d'infectiologie** | Visite de suivi VIH habituelle | | Visites de suivi VIH habituelle[†] | Visites de suivi VIH habituelle |
| Bilan VIH standard | x | | x | x |
| Pré-inclusion :<br>- Vérification des critères d'éligibilité<br>- Information du participant | x | | | |
| **Service de proctologie** | | Visite d'inclusion | Visites de contrôle | Visites de suivi |
| Inclusion :<br>- Vérification des critères d'éligibilité<br>- Information du participant<br>- Signature du consentement éclairé | | x | | |
| Interrogatoire d'inclusion | | x | | |
| Interrogatoire de suivi | | | a | x |
| Examen procto. avec frottis anal | | x | a | x |
| Examen cytologique (frottis anal) : cellules exfoliées épithélium anal | | x | a | x |
| Biothèque : cellules exfoliées épithélium anal | | x | a | x |
| Biothèque : extractions d'acides nucléiques de cellules exfoliées épithélium anal | | x | a[d] | x[d] |
| Examens biologiques : détection et génotypage ADN HPV | | x | a[d] | x[d] |
| Autres examens biologiques 1 (Rennes) : coloration p16/Ki-67 | | x | | |
| Autres examens biologiques 2 (Amsterdam) : méthylation de gènes CADM1, MAL | | x | | |
| Examen para clinique : anuscopie haute résolution (AHR) | | x | a | x[e] |
| Biopsie et examen histologique (si lésion évocatrice d'AIN à l'AHR) | | x | c | x[e] |

* le cas échéant ; cf. protocole 9.5 pages 26 et 27
† visite habituelle libérale ou hospitalière
**a** uniquement pour sujets diagnostiqués avec lésions haut-grade (ASC-H, HSIL ou AIN2/3) lors d'une visite précédente
**b** uniquement pour sujets diagnostiqués avec lésions haut-grade (ASC-H, HSIL ou AIN2/3) lors de la même visite (sauf visites postérieures à M24)
**c** uniquement en cas de nouvelles lésions ou modification importante d'une lésion détectée à la visite précédente
**d** uniquement pour les visites de suivi réalisées avant le 1e juillet 2018
**e** à partir du 1e juillet 2018, AHR (et biopsie si nécessaire) uniquement pour les participants ayant eu une lésion de haut-grade (ASC-H, HSIL ou AIN2/3) détectée au cours d'au moins une visite protocolaire antérieure





## B - How to access the collection

1- project submission: **via the sample request form on the website**

2- project evaluation: **scientific committee**

3- Making the collection available**: final decision by ANRS MIE management**

Contact e-mail address for submitting your project: **biobanque@anrs.fr**